DOCKET NO.: CP380H **PATENT**
Application No.: 10/789,628
Office Action Dated: July 11, 2006

REMARKS

Following entry of the foregoing amendments, claims 1, 3 to 12, and 20 will be pending in the application. Claims 1, 3 to 9, 12, and 20 have been amended, and claims 2 and 13 to 19 have been canceled, herein, without prejudice. No new claims have been added. Support for the amendments is found throughout the specification as originally filed. No new matter has been added.

Applicants respectfully request reconsideration of the rejections of record in view of the foregoing amendments and the following remarks.

Alleged Obviousness

A. Claims 1 to 13, 18, and 20 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the combined teachings of U.S. Patent No. 6,720,011 ("the Zhang patent") and Sacchi, S., *et al.*, *Haematologica* 82, 1997, 106-121 ("The Sacchi article") in view of Chinese Patent number CN 1121807 ("the 807 patent") and Shimotsuura, S., *Journal of Tokyo Dental College Society*, 1986, 86(8) 1237-1253 ("the Shimotsuura article"). Applicants respectfully request reconsideration and withdrawal of the rejection because the Office has failed to establish *prima facie* obviousness.

To establish *prima facie* obviousness, the Patent Office must provide ***objective evidence*** that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains some suggestion or incentive that would have motivated those of ordinary skill in the art to modify a reference or to combine references. "The mere fact that references ***can*** be combined or modified does not render the resultant combination obvious ***unless the prior art also suggests the desirability of the combination***." M.P.E.P. § 2141.03 (citing *In re Mills*, 916 F.2d 680 (Fed. Cir. 1990), emphasis added).

Prior art references that serve as the basis of an obviousness rejection must be considered by the Patent Office in their entirety, *i.e.*, ***the references must be considered as a whole,*** including portions that would lead away from the claimed invention. M.P.E.P. 2141.02 (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)).

Applicants respectfully submit that the Office has failed to demonstrate that those of ordinary skill in the art would have been motivated to combine the teachings of the cited

references. In fact, the Sacchi article ***teaches away*** from its combination with the remaining references because it indicates that all-trans retinoic acid (ATRA) had not been proven effective as a treatment for lymphoma. Specifically, the article describes two studies in which ATRA was administered to lymphoma patients. In the first study, 13 patients with refractory cutaneous T-cell lymphomas were treated with oral ATRA. Only four of the patients achieved a partial remission. In the second study, L-ATRA was administered intravenously to patients with different hematologic malignancies. Three patients with cutaneous T-cell lymphomas resistant to a prior retinoid displayed only a minor, transient response to the L-ATRA, and only one of four disseminated T-cell lymphoma patients achieved a partial remission. The Sacchi article thus reports studies in which only a small minority of lymphoma patients that received ATRA were able to achieve a partial or minor and transient remission. The article, therefore, indicates that ATRA was not effective at causing remission in more than a small minority of lymphoma patients that received the ATRA, and, moreover, the remission was only partial or transient in those patients.

Upon review of the Sacchi article, those skilled in the art would thus not have been motivated to use ATRA to treat lymphoma, and, accordingly, would not have been motivated to treat lymphoma by combining ATRA with other possible lymphoma therapies. For example, those skilled in the art would not have been motivated to combine the teachings of the Sacchi article with those of the Zhang and 807 patents and the Shimotsuura article. The Zhang patent describes arsenic trioxide compositions[1] and states that arsenic trioxide can be used to treat leukemia, hepatoma, and lymphoma (col. 1, ln. 35). The patent fails to teach or suggest that ATRA can be used to treat lymphoma, however. Moreover, the patent's single working example describes the use of arsenic trioxide compositions for the treatment of a particular type of leukemia (acute promyelocytic leukemia) (col. 2. ln. 59 to col. 3, ln. 27), rather than lymphoma. In addition, the patent's description of the effect of the described arsenic trioxide compositions on cancer cells is limited to a description of its effect on leukemia cells:

> Laboratory experiments indicate that the composition shows a strong abruptive effect on the membranes of leukemic cells. It also inhibits DNA/RNA synthesis in such cells, reduces the rate of proliferation of leukemic cells and destroys the leukemic cells.

[1] "The present invention is directed to an intravenous drip composition for the treatment of cancers. The cancers treatable include leukemia, hepatoma and lymphoma." (col. 1, lns. 33 to 35).

(col. 2, lns. 23 to 27).

The 807 patent describes the efficacy of Ai Ling, which contains arsenic trioxide, sodium chloride, and water, for the treatment of leukemia and suggests that Ai Ling can be used to treat lymphatic cancer. Notably, however, while the patent describes the effects that Ai Ling has against leukemia cells, it does not describe any such effect against lymphatic cancer cells:

> Tests have proven that this drug has strong effects on the destruction of leukemia cell membranes, inhibiting DNA and RNA synthesis and loss of ability of clone proliferation; in vivo and in vitro tests have verified that it possessed marked killing effects against leukemia cells; it also has effects which induce the leukemia cells to differentiate to normal cells; it is able to promote the restoration of bone marrow hemopoietic functions...[2]

In addition, the experimental examples provided in the patent describe the effects of administering Ai Ling to patients suffering from acute promyelocytic leukemia, not to patients suffering from lymphatic cancers. Thus, the patent does not describe, teach, or suggest treatment of lymphoma with ATRA.

The Shimotsuura article describes the efficacy of arsenic trioxide in a mouse sarcoma model and indicates that arsenic trioxide was only efficacious when it was coadministered with an antidote. Although the Office action asserts that the article teaches that "antineoplasmic [*sic*] actions of arsenic trioxide are primarily achieved by DNA composition blockage,"[3] the article states that the DNA composition blockage occurred in the S-180 (sarcoma) cells transplanted into the mice, and does not teach that DNA composition blockage occurs in cancerous cells other than sarcoma cells:

> From above results, As_2O_3 is considered that can increase life span of the mouse by blocking DNA composition of S-180 cells and protein composition.[4]

Moreover, the article fails to teach or suggest treating lymphoma with ATRA.

Assuming *arguendo*, which Applicants do not concede, that those skilled in the art would have been motivated to treat lymphoma with arsenic trioxide based upon the teachings of the Zhang and 807 patents and the Shimotsuura article, those skilled in the art would not have been motivated to combine the teachings of the Zhang and 807 patents and the Shimotsuura article

[2] Page 5 of the English translation.
[3] Office action dated July 11, 2006, page 6.
[4] Page 20 of the English translation.

with those of the Sacchi article, as discussed above, and thus would not have been motivated to treat lymphoma with a combination of arsenic trioxide and ATRA.

Although the Office asserts that those of ordinary skill in the art would have been motivated to combine arsenic trioxide and ATRA to treat lymphoma because combination therapies are conventional practice in the cancer treatment field and ATRA was known to have activity against lymphomas,[5] as discussed above, the Sacchi article indicates that ATRA had not proven effective as a treatment for lymphoma, resulting in only a partial or transient remission in a minority of lymphoma patients that received ATRA. Since those skilled in the art would not have been motivated to treat lymphoma with ATRA, those skilled in the art would not have been motivated to treat lymphoma with a combination of ATRA and other possible lymphoma therapeutics. Accordingly, those skilled in the art would not have been motivated to combine the teaching of the Zhang and 807 patents and the Shimotsuura article with those of the Sacchi article, and the Office has thus failed to establish *prima facie* obviousness. Applicants accordingly, respectfully, request withdrawal of the rejection.

B. Claims 1 to 13, 18, and 20 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over the combined teachings of the Zhang patent and the Sascchi article in view of the 807 patent, Li, *et al.*, *Chinese J. Oncology*, 10, 1988, 61062 ("the Li article"), and the Shimotsuura article. Applicants respectfully traverse the rejection as it appears to be based on the assumption that those of ordinary skill in the art would have been motivated to combine the teachings of the Zhang patent, the Sascchi article, the 807 patent and the Shimotsuura article. Because this assumption is believed to be incorrect, as discussed above, Applicants respectfully request withdrawal of the rejection.

[5] Office action dated July 11, 2006, page 7.

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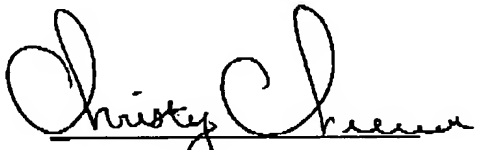
Alleged Double Patenting

Claims 1 to 13, 18, and 20 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1, 3 to 11, 13 to 17, 19, and 20 of copending U.S. patent application number 10/649,944 in view of the Sacchi article. Since this rejection is a provisional rejection due to the fact that the allegedly conflicting claims have not yet been patented, Applicants respectfully request deferral of the rejection pending the identification of allowable subject matter, as it can likely be readily resolved (depending upon the subject matter ultimately allowed) through the filing of a suitable terminal disclaimer.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable action is respectfully requested.

Respectfully submitted,



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